CASE REPORT

Gorlin-Goltz syndrome in twin brothers: an unusual occurrence with review of the literature

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Accepted 4 August 2015

SUMMARY

Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome, is caused by genetic alteration produced by a mutation in the 'patched' tumour suppressor gene, and is inherited in a dominant autosomal way. Although sporadic cases have been found, this syndrome has rarely been reported in twin patients. The syndrome is characterised by a wide range of developmental abnormalities and has a predisposition to neoplasms such as multiple pigmented basal cell carcinomas and keratocysts in jaws; it also has other features such as palmar and/or plantar pits and calcification of falx cerebri. Owing to the critical oral and maxillofacial manifestations of this syndrome, it is important to recognise its characteristics in order to make a diagnosis, and to plot early preventive treatment and establish the right genetic evidence. Based on a combination of imaging, clinical and histopathological findings, we present a diagnosed case of Gorlin-Goltz syndrome in 18-year-old twin brothers. All cystic lesions were enucleated and 1 year follow-up showed no recurrence.

BACKGROUND

Gorlin-Goltz syndrome is rarely seen and extremely rare in twins. Only a handful of Gorlin-Goltz syndrome cases have been reported in the literature; to the best of our knowledge, ours is the first case report of the syndrome in twin brothers reported in India. We would like to share this report with other oral and maxillofacial clinicians through this journal.

CASE PRESENTATION

Patient A: An 18-year-old man presented with swelling over the left middle third and right lower third region of the face for 3 months. General examination showed a solitary sebaceous cyst on the skin of the third toe of the right foot ([figure 1](#)) and presence of multiple palmar pits ([figure 2](#) and showing mild hypertelorism ([figure 3](#)).

An extraoral examination ([figure 3](#)) showed a single diffuse approximately 3×2 cm swelling present over the left maxillary region extending from the lateral part of nares to the cheek region; the swelling was soft to firm, non-tender and non-fluctuant on palpation. A second swelling ([figure 4](#)), approximately 3×3 cm, over the right ramus region of the mandible, was soft, non-tender and non-fluctuant on palpation. Slight frontal bossing was also present. Submandibular lymph nodes were palpable on the right side. Based on clinical findings, a provisional diagnosis of dentigerous cyst was

Figure 1 Solitary sebaceous cyst over the skin of third finger.

made. The orthopantomogram (OPG; [figure 5](#)) showed multiple expansile radiolucencies associated with impacted teeth 23 and 48, and a radiolucency associated with periapical region of teeth 15 and 16. In order to confirm the extent of the cystic lesions, axial ([figure 6](#)) and coronal ([figure 7](#)) CTs, and three-dimensional (3D) reconstruction ([figures 8 and 9](#)) were carried out, showing multiple lesions involving the right ramus of the mandible and left anterior, posterior region of the maxilla, which were radiolucent and expansile, causing thinning of

Figure 2 Presence of multiple palmar pits.

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To cite: Anchlia S, Vyas S, Bahl S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211608

Figure 3 Mild hypertelorism and diffuse swelling on left anterior maxillary region.

Figure 4 Diffuse swelling present over right mandibular region.

Figure 5 Multiple expansile radiolucencies associated with impacted teeth.

Figure 6 Axial CT with multiple lesions in mandible and maxilla.

Figure 7 Coronal CT with radiolucent lesion in right ramus of mandible.

Figure 8 Three-dimensional reconstruction with lesion involving ramus of mandible.

Figure 9 Three-dimensional reconstruction with radiolucency involving left maxilla.

the cortex. There was no breach in the cortex and no evidence of calcification was seen.

All preoperative investigations were undertaken and a medical fitness report was obtained from the patient's physician. All the

Figure 11 Gross cystic lesion on right mandible region.

Figure 12 Gross cystic lesion over left posterior maxilla region.

three lesions were enucleated under general anaesthesia followed by use of Carnoy's solution in the cavities. Pathological specimens were obtained ([figure 10](#) left anterior maxillary region; [figure 11](#) right mandibular ramus region; [figure 12](#) left posterior maxillary region). The gross appearance of the lesions was soft in consistency and creamy-brown in colour, with irregular borders. The histopathological features ([figure 13](#), H&E stain, $\times 10$) showed cystic lumen filled with lamellated

Figure 10 Gross cystic lesion on left maxillary region.

Figure 13 Cystic lumen filled with keratin (H&E stain, $\times 10$).

Figure 14 Cystic lining, 4–6 cells thick (H&E stain, $\times 20$).

keratin flecks. The cystic lumen was covered with a cystic lining that was corrugated parakeratinised stratified squamous epithelium, 2–8 cells thick, and the underlying cystic wall, which was loosely arranged, was fibrocellular in nature with scattered inflammatory cells. Higher magnification (figure 14, H&E stain, $\times 20$) of the cystic lining showed a palisaded row of basal cells with reverse basal polarity and a flat epithelium connective tissue junction. The cystic wall showed fibrocellular connective tissue stroma with scattered inflammatory cells; these histopathological features were common to all the three pathological specimens. The histopathological diagnosis of multiple

Figure 16 X-ray posteroanterior, chest view, showing spina bifida with third bifid rib of right side.

Figure 15 X-ray antero-posterior, skull view, showing falx cerebri calcification.

Figure 17 Extraoral examination, with no abnormality seen.

Figure 18 Intraoral examination, with no abnormality seen.

odontogenic keratocyst (OKC) was made. In suspicion of Gorlin-Goltz syndrome, an X-ray antero-posterior (AP), skull view (figure 15), was taken, which showed falx cerebri calcification and X-ray PA, chest view (figure 16), showed spina bifida at D1 and D2 with third bifid rib of right side. Correlating with clinical, radiological and histopathological findings, a diagnosis of Gorlin-Goltz syndrome was made.

Patient B: Patient A's twin brother presented for a routine dental check-up and radiological examination was performed to rule out the possibility of Gorlin-Goltz syndrome. Extraoral (figure 17) and intraoral examinations (figure 18) showed absence of abnormal findings; however, there was absence of all four wisdom teeth: 18, 28, 38 and 48. On general examination, palmar (figure 19) and plantar pits (figure 20) were noticed and there was presence of mild to moderate hypertelorism (figure 17). X-ray anteroposterior, skull view, was taken (figure 21), showing falx cerebri calcification and X-ray, dorsal spine view (figure 22), showed evidence of kyphus deformity with scoliosis towards the left. OPG (figure 23) showed multiple expansile radiolucent lesions present in the left and the right mandible, and in the maxilla. These lesions involved the angle, body of mandible and posterior region of the maxilla, with all the four impacted wisdom teeth. Coronal (figure 24) and axial (figure 25) CTs showed evidence of lytic lesions involving the right and the left mandible, as well as the maxilla. All preoperative investigations were carried out and a medical fitness report was obtained from the patient's physician. All the four cystic expansile lesions

Figure 19 Palmer pits are evident.

Figure 20 Plantar pits are evident.

were enucleated under general anaesthesia, followed by application of Carnoy's solution. Pathological specimens were obtained (figure 26 right maxilla; figure 27 left maxilla; figure 28 left mandible; figure 29 right mandible) and exhibited a gross appearance of the cystic lesions, with the attached teeth; the lesions were soft in consistency and creamy-brown in colour, with irregular borders. The histopathological examination of the specimens showed cystic lumen filled with keratin flecks (figure 30, $\times 10$ (H&E stain) and lumen covered with cystic lining, 4–6 cells thick, showing parakeratinised stratified squamous epithelium with a corrugated appearance. The basal layer of cystic lining had a tombstone appearance with the basal cell layer showing reverse polarity. The underlying cystic wall showed fibrocellular connective tissue stroma with spindled fibroblast intermixed with scattered inflammatory cells. The overall features were suggestive of OKCs, which were common in all the cystic lesions except for

Figure 21 X-ray anteroposterior, skull view, showing falx cerebri calcification.

Figure 22 X-ray report showing kyphus deformity and scoliosis on the left.

that of the right mandible, which was showing hyperplastic parakeratinised stratified squamous epithelium. Correlating clinically, radiologically and histopathologically, confirmation of Gorlin-Goltz syndrome in the twin brothers was made. The parents of the patient were examined and underwent radiological evaluation; neither had any features of Gorlin-Goltz syndrome.

INVESTIGATIONS

- ▶ OPG
- ▶ CT (axial, coronal sections of mandible, maxilla)
- ▶ 3D reconstructions (craniofacial structures)
- ▶ X-ray PA, skull view, in anticipated falx cerebri calcifications
- ▶ X-ray PA, chest view, in anticipated bifid ribs
- ▶ Histopathology examination

For better definition and extension of the cystic swellings, they were judged by different CT scan views and 3D reconstructions for bony destructions.

Figure 23 Orthopantomogram showing multiple radiolucent lesions with all four wisdom teeth.

Figure 24 Coronal CT showing evidence of lytic lesion in mandible and maxilla.

DIFFERENTIAL DIAGNOSIS

Because of multiple radiolucencies associated with impacted teeth, working diagnoses were given:

1. Dentigerous cyst irt (48, 23);
2. Keratocystic odontogenic tumour irt (48, 23) due to unilocular radiolucencies;
3. Gorlin-Goltz syndrome correlating with clinical and radiological findings, and general body examination.

And lastly, a differential diagnosis of unicystic ameloblastoma and/or dentigerous cyst was made.

TREATMENT

The therapeutic techniques for keratocysts vary from simple enucleation with curettage, to enucleation with peripheral osteotomy or en bloc resection. There are also more conservative options such as local parietal therapy with Carnoy's solution, cryotherapy or marsupialisation of the cysts, or through decompression followed by a secondary enucleation.¹

All the seven cystic expansile lesions (three in patient (A) and four in patient (B)) were enucleated followed by application of Carnoy's solution. Owing to multiple radiolucencies, resection was not carried out.

Postoperatively, both patients recovered normally and, during the follow-up period, both patients were asymptomatic.

Figure 25 Axial CT showing evidence of lytic lesion in both right and left mandible.

Figure 26 Gross cystic lesion over right maxilla with tooth.

OUTCOME AND FOLLOW-UP

Postoperatively, the surgical site healed uneventfully, with no complications in either patient; they recovered well with no signs of neurosensory deficit. Follow-up of 1, 3 and 6 months, and 1 year, showed no recurrence and they remained asymptomatic.

DISCUSSION

The term 'twins' most notably refers to two siblings who have shared the same uterus (womb) and are usually but not necessarily born on the same day. Twins may be monozygotic (identical) or dizygotic (non-identical). Monozygotic twins are genetically identical, unless there has been a mutation in development, and they are almost always the same gender. Monozygotic twins generally look alike—sometimes to the extent that they appear as mirror images of each other. Monozygotic twinning occurs in approximately 0.25% of human births.² Monozygotic twins arise from same zygote, whereas dizygotic twins arise from a pair of separate eggs, fertilised by two different sperms. As a result, monozygotic twins have the same chromosomal DNA sequence, except for very small errors of DNA replication after the four to eight cell zygote stages. Monozygotic twins share their entire nuclear DNA, whereas dizygotic twins share only 50% of DNA sequence variation, on average.³

Human monozygotic twins and other genetically identical organisms are almost always strikingly similar in appearance, yet they are often discordant for important phenotypes including complex diseases. Such variation among organisms with

Figure 27 Gross cystic lesion over left maxilla with tooth.

Figure 28 Gross cystic lesion over left mandible with tooth.

Figure 29 Gross cystic lesion over right mandible with tooth.

virtually identical chromosomal DNA sequences has largely been attributed to the effects of environment or epigenetic factors.³

Epigenetics refers to DNA and chromatin modifications that play a critical role in regulation of various genomic functions. Although the genotype of most cells of a given organism is the same (with the exception of gametes and the cells of the immune system), cellular phenotypes and functions differ radically, and this can be (at least to some extent) controlled by

Figure 30 Cystic lumen, cystic lining and wall (H&E stain, ×10).

Figure 31 Epigenetic model of monozygotic twin discordance in complex disease, eg, schizophrenia. Red circles represent methylated cytosines. From the epigenetic point of view, phenotypic disease differences in monozygotic twins result from their epigenetic differences. Owing to the partial stability of epigenetic signals, a substantial degree of epigenetic dissimilarity can be accumulated over millions of mitotic divisions of cells of monozygotic co-twins. Although the figure shows that disease is caused by gene hypomethylation, scenarios where pathological condition is associated with gene hypermethylation are equally possible.

differential epigenetic regulation that is set up during cell differentiation and embryonic morphogenesis.³

Epigenetic mechanisms can easily be integrated into a model of phenotypic variation in multicellular organisms, which can explain some of the phenotypic differences among genetically identical organisms. Monozygotic twin discordance for complex, chronic, non-Mendelian disorders such as schizophrenia, multiple sclerosis or asthma, could arise as a result of a chain of unfavourable epigenetic events in the affected twin. During embryogenesis, childhood and adolescence, there is ample opportunity for multidirectional effects of tissue differentiation, stochastic factors, hormones and, probably, some external environmental factors (nutrition, medications, addictions, etc) to accumulate in only one of the two identical twins (figure 31).³

The diagnosis of Gorlin-Goltz syndrome is made clinically by using the criteria that is suggested by Evans and others. Two major or one major and two minor criteria should be satisfied for a positive diagnosis⁴ (table 1).

In our twin patients, diagnosis of Gorlin-Goltz syndrome was established based on presence of major and minor criteria present in the twins (table 2).

Although multiple OKCs can occur as a part of some rare dermatological syndromes, such as Bazex syndrome (rare acral

psoriasiform dermatosis, internal malignancy, carcinoma of upper aerodigestive tract) or Torre's syndrome (skin sebaceous tumours with internal malignancy), our patients were apparently healthy and had no features suggestive of these syndromes.⁵

The previous literature states that basal cell carcinoma is a disorder of white individuals, especially those with very fair skin. It is rare in dark-skinned individuals.⁶ Both the twins were dark skinned and this melanin pigmentation could have been responsible for absence of basal cell carcinoma in these patients. Data from the literature indicate that Gorlin-Goltz syndrome is very rarely seen in twins; to the best of our knowledge, this is the first such report from India. Radiographically, OKCs present as well-defined radiolucent lesions with smooth, usually corticated margins, and may either be multilocular or unilocular. They may present with scalloped borders, indicative of a varying growth pattern. In most cases, there is involvement of an unerupted tooth with no apparent root resorption.¹ In both the cases described above, there were unerupted teeth associated with well-defined unilocular radiolucencies.

Studies have shown that parakeratinisation, intramural epithelial remnants and satellite cysts are more frequent among OKCs associated with nevoid basal cell carcinoma syndrome (NBCCS) than in solitary keratocysts.¹ In both the cases, the lining of the OKCs revealed the presence of parakeratinisation and absence of developing microcysts in the connective tissue wall. Table 3 describes the characteristics of NBCCS-associated and non-NBCCS-associated OKCs¹.

In the present case of Gorlin-Goltz syndrome, it was imperative to make a timely diagnosis, since the severity of complications, such as skin and brain malignant tumours, can be reduced, and the destruction and secondary oral maxillofacial

Table 1 Major and minor criteria to diagnose Gorlin-Goltz syndrome

Major criteria	Minor criteria
<ul style="list-style-type: none"> Multiple basal cell carcinoma occurring under the age of 20 years Histologically proven OKCs of the jaws Palmar and plantar pits (three or more) Bilamellar calcification of the falx cerebri Bifid, fused or markedly splayed ribs First-degree relative with nevoid basal cell carcinoma syndrome 	<ul style="list-style-type: none"> Macrocephaly (adjusted for height) Congenital malformation: cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism Other skeletal abnormalities: Sprengel deformity, kyphoscoliosis, marked pectus deformity, marked syndactyly of the digits Radiological abnormalities: bridging of sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of vertebral bodies, modelling defects of hands and feet or flame-shaped hands or feet Ovarian fibroma Medulloblastoma

OKCs, odontogenic keratocysts.

Table 2 Comparison of features of both patients

Patient A	Patient B
Major criteria <ul style="list-style-type: none"> Multiple odontogenic keratocyst Bifid ribs, palmar pits Falx cerebri calcification 	Major criteria <ul style="list-style-type: none"> Multiple odontogenic keratocyst Palmar plantar pits Falx cerebri calcification
Minor criteria <ul style="list-style-type: none"> Sebaceous cyst, hypertelorism Wide nasal bridge, spina bifida Frontal bossing 	Minor criteria <ul style="list-style-type: none"> Scoliosis, hypertelorism Wide nasal bridge

Table 3 Comparison of clinical and histological features of nevoid basal cell carcinoma syndrome (NBCCS) associated and solitary odontogenic keratocysts (OKCs)

NBCCS-associated OKCs	Solitary OKCs
Clinical characteristics	
Occur at early age	Occur at middle or old age
Multiple cysts	Isolated cysts
Occur equally in both jaws	Occurs more often in the lower jaw
Frequency	
High recurrence rate (82%)	Lower recurrence rate (61%)
Histological characteristics	
Smaller epithelial height	Greater epithelial height
Fewer total and basal nuclei	More total and basal nuclei
More frequent occurrence of odontogenic islands, daughter cysts and odontogenic islands	Less frequent occurrence of odontogenic islands

deformities of the jaw cysts can be avoided, if addressed early. Also, an early diagnosis is important to gather adequate genetic information. Patients suffering from this syndrome must undergo check-ups at least once a year, especially those patients with OKCs.⁷ The ideal treatment for OKCs is enucleation or curettage followed by treatment of the cavity with an agent that can destroy the epithelial remnants or satellite cysts (such as Carnoy's solution). Segmental resections are performed in cases with highly aggressive lesions and/or soft tissue invasion. In add-

ition, the osseous framework should be left intact to allow for osteoconduction. The use of Carnoy's solution or liquid nitrogen cryosurgery following enucleation helps prevent recurrences.¹ Our syndromic patients were kept under follow-up, with their last follow-up, which showed no recurrence, completed 1 year after treatment.

Learning points

- ▶ Gorlin-Goltz syndrome is a dominant autosomal genetic pathology that is of particular interest to oral and maxillofacial health experts.
- ▶ Odontogenic keratocysts are frequently the presenting manifestation of this syndrome.
- ▶ Once the diagnosis is established, it is important to follow-up patients for the rest of their lives and recommend genetic counselling for all their other family members.

Acknowledgements Special thanks to Dr Swapan Goswami (MD, pathologist), professor, Department of Pathology, SBKS Medical College, Vadodara, Gujarat, India; Dr Mohit Gupta (MD, radiologist), private practitioner; Dr Arvind Agarwal (MD, radiologist), private practitioner; and Dr Surabhi Sinha (PG II student, Department of Oral and Maxillofacial Pathology, KM Shah Dental College, Vadodara, Gujarat, India, for their technical support to this case report.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

- ▶ (Patient A): I came to hospital because of swelling over the left middle third and right lower third region of my face for 3 months. After being diagnosed and getting operated on, I am well and the swelling has completely subsided.
- ▶ (Patient B): With a suspicion of having the same problem my brother had, I came to hospital for a check-up. I was found to also be suffering from the problem; after being operated on, I remain well.
- ▶ We both look forward to investigations to be carried out in our five other brothers.

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